EXHIBIT 21

REMARKS

This is further in Response to the outstanding Final Rejection of September 22, 2004, and Applicants' Notice of Appeal of March 18, 2005. Applicants wish to supplement the record to clarify their position and to address characterizations of the cited art presented in support of the outstanding rejections.

This Request for Continued Examination includes a submission of a new claim 47, which recites objective criteria for the dissolution of a composition of the present invention. The criteria are supported by the Examples, notably Example 1, wherein it is further stated the dissolution is measured according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1N.

DeBoeck et al., USPN 5,545,628:

Applicants traverse the outstanding rejection over DeBoeck.

DeBoeck is directed to fenofibrate formulations compounded from molten fenofibrate. This necessarily excludes micronized fenofibrate as recited in claim 1. Although DeBoeck describes formulations having 5-95% fenofibrate, the reference does not teach or suggest a formulation meeting the limitations of the instant claims. DeBoeck does not teach or suggest formulations having micronized fenofibrate in an amount greater than or equal to 60% by weight and a binding cellulose derivative between 2 – 15% by weight.

In fact, DeBoeck states that an objective was the formation of a fenofibrate formulation that eliminates the need for micronization:

> Accordingly, it is an object of the present invention to provide a fenofibrate formulation not requiring use of co-micronization

> which, nevertheless, exhibits a bioavailability comparable to formulations of fenofibrate which do.
>
> It is also an object of the present invention to provide a solid, oral dosage form of a fenofibrate formulation that can be prepared by melting the excipients in which the fenofibrate is soluble and, therefore, does not require any particle size specification.

DeBoeck, column 2, lines 12-20 (emphasis added).

Further, DeBoeck states that the process is "particularly advantageous" in its simplicity; and that "[T]his renders the present manufacturing process extremely cost effective when compared to one using co-micronization of powders." DeBoeck, col. 2, lines 61-67.

DeBoeck repeatedly contrasts the disclosed formulation and method from those using micronized fenofibrate. DeBoeck repeatedly states that they deliberately sought to avoid the use of co-micronization, and that the resulting ability to compound a formulation by melting rather than co-micronization is "particularly advantageous." DeBoeck states that they were able to achieve those objectives by, among other things, resorting to the addition of specific types and quantities of, e.g., a suspension stabilizer.

The present invention is expressly limited to micronized fenofibrate. By DeBoeck's own reasoning, a formulation and method using micronization is materially distinct from that disclosed by DeBoeck. Indeed, DeBoeck teaches away from Applicants' claimed invention. It is axiomatic that a reference that teaches away from a claimed invention cannot render it obvious.

Furthermore, the outstanding rejection states that DeBoeck teaches fenofibrate formulations with high amounts of surfactants and disintegrating agents, such as polyols and poloxamers. Applicants respectfully submit that those

compounds belong to a different chemical class than the claimed hydrophilic polymers, e.g., hydroxypropylmethylcellulose (HPMC).

In DeBoeck, the polyols and poloxamers are used as a suspension stabilizer, which "avoids the formation of fenofibrate crystals during the cooling of the filled hard gelatin capsules." DeBoeck, column 2, lines 44-48. In contrast, the claimed invention uses micronized fenofibrate, for which there would be no need to avoid such crystallization, and thus there would be no motivation to add such stabilizers. Consequently, there is nothing in DeBoeck that would have motivated one of ordinary skill in the art to incorporate such stabilizers in a formulation of micronized fenofibrate.

Finally, DeBoeck discusses the use of suspension stabilizers in a molten mixture of fenofibrate-polyglycolyzed glycerides. The quantity of suspension stabilizer is about the same as that of the fenofibrate. In the present invention, however, the amount of surfactant is much lower than the amount of fenofibrate (e.g., about an order of magnitude). Thus, the ratios of the various components are different between DeBoeck and the present invention, and DeBoeck does not teach or suggest the claimed formulations.

Stamm et al., USPN 6,074,670:

Applicants traverse the rejection based upon Stamm.

The Stamm reference discloses an immediate release fenofibrate composition comprising:

(a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 µm, a hydrophilic polymer and a surfactant; and

(b) optionally one or several outer phase(s) or layer(s),

wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45" by weight, said hydrophilic polymer makes up from 20 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight.

The most recent Advisory Action mischaracterizes applicants' statements regarding the relevance of Stamm. Applicants did not state that the instant subject matter is not patentable absent evidence of criticality of the percentages. Quite to the contrary. Applicants quoted the MPEP stating that differences in ranges will not support patentability when subject matter is encompassed by the prior art unless the range is shown to be critical. Applicants plainly argued that such is not the case. Stamm does not encompass, nor does it abut, the claimed ranges. Thus, no showing of criticality is required.

In fact, Stamm teaches away from the claimed invention. Stamm unequivocally teaches that the hydrophilic polymer must be at least 20% by weight. (Stamm, col. 3, lines 11-23). Applicants claim that the corresponding element must be between 2 – 15% by weight. This is not only well outside the range taught by Stamm, it goes squarely against the teaching of Stamm. Thus, patentability of the claimed range does not require any showing of criticality.

The Advisory Action would ignore that teaching from Stamm. It states that Stamm teaches the same active agent and the same polymers, and then makes an

unsupported inference that Stamm encompasses the invention. But it does not. Rather, the inference and the argument ignore the plain teaching of the reference, and fail to consider the reference as a whole. The reference very plainly teaches that the immediate-release fenofibrate composition must have a hydrophilic polymer component making up at least 20% by weight. *E.g.*, col. 3, lines 12-20. There is simply nothing in the reference to the contrary that would support the rejection.

Indeed, Stamm distinguishes its formulations from those of EP 0 330 532. EP '532 describes formulations wherein fenofibrate is co-micronized with a solid surfactant, e.g., sodium lauryl sulfate. According to USPN 4,895,726, which is related to EP 0 330 532, it is possible to improve bioavailability of fenofibrate to a significantly greater extent than would be achieved either by adding a surfactant, or by micronizing the fenofibrate on its own, or by intimately mixing the separately micronized fenofibrate and surfactant. USPN 4,895,726, col. 1, lines 35-43. In Stamm, co-micronization with a solid surfactant is eliminated by introducing at least 20% by weight hydrophilic polymer.

The Stamm reference does not teach or suggest formulations using less hydrophilic polymer; nor does it teach or suggest that a similar effect can be achieved by balancing less hydrophilic polymer while retaining co-micronization with some surfactant. Stamm does seem to suggest that the two phenomena can be used together, but even when combined, the reference does not suggest reducing the minimum requisite quantity of hydrophilic polymer (i.e., below the stated minimum of 20 wt %). Accordingly, Stamm does not teach or suggest a micronized fenofibrate formulation comprising less than 20 wt % hydrophilic polymer, and so does not encompass (or abut) the present invention.

In view of the foregoing remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: May 18, 2005

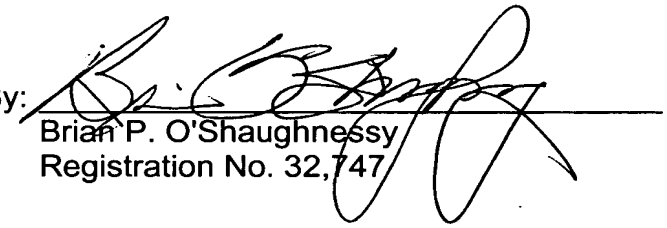
By: 
Brian P. O'Shaughnessy
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EXHIBIT 22

Interview Summary	Application No. 10/030,262	Applicant(s) CRIERE ET AL.	
	Examiner Lakshmi S. Channavajjala	Art Unit 1615	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Lakshmi S. Channavajjala*.

(2) *Brian O'Shaughnessy*.

(3) *Pascal Oury*.

(4) *Nadine Rocaboy*.

(5) Richard Berman

(6) George Bobotas

Date of Interview: *20 September 2005*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *on record*.

Identification of prior art discussed: *on record*.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Discussed the in vivo bioavalability data presented during the interview, comparing the formulations of Stamm et al and Curtet et al, with a composition that is within the scope of the instant invention. Instant formulation shows an increase in the bioavalability of the drug as opposed to the prior art formulations. Applcants will present a declaration showing the unexpected increase in bioavailability. Applicants will further amend claim 1 to recite a granule form and seperately limit the composition to the mass ratios of claim 21. Claims 38-46 will be canceled without prejudice. Applicants response and submission will be given consideration in determining the patentability of the claims.

EXHIBIT 23

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Currently Amended) A pharmaceutical composition ~~comprising~~in the form of granules, wherein each granule comprises a neutral microgranule on which is disposed a composition comprising: micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization adjuvant, and

wherein said fenofibrate is present in an amount greater than or equal to 60% by weight, relative to the weight of ~~the~~said pharmaceutical composition, and further wherein said binding cellulose derivative represents between 2 to 15% by weight, relative to the weight of ~~the~~said pharmaceutical composition.

2. (Currently Amended) The pharmaceutical composition of claim 1, wherein said binding cellulose derivative is hydroxypropylmethylcellulose.

3. (Currently Amended) The pharmaceutical composition of claim 2, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 18 cP.

4. (Currently Amended) The pharmaceutical composition of claim 1, wherein said fenofibrate is present in an amount greater than or equal to 70% by weight, relative to the weight of ~~the~~said pharmaceutical composition.

5. (Currently Amended) The pharmaceutical composition of claim 1, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

6. (Currently Amended) The pharmaceutical composition of claim 1, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of ~~the~~said fenofibrate.

7. (Currently Amended) The pharmaceutical composition of claim 2, wherein said fenofibrate/HPMC mass ratio is between 5/1 and 15/1.

8. (Cancelled)

9. (Currently Amended) The pharmaceutical composition of claim 1, wherein said pharmaceutical composition further comprises at least one excipient.

10. (Currently Amended) The pharmaceutical composition of claim 1, wherein said micronized fenofibrate has a mean particle size less than 15 μm.

11. (Currently Amended) The pharmaceutical composition of claim 1, wherein said composition is ~~in the form of powder or granules, optionally~~ contained in gelatin capsules.

12. (Currently Amended) A method for preparing the pharmaceutical composition of claim 1 ~~11~~, wherein said granules are prepared by ~~assembly on neutral microgranules, by~~ spraying onto neutral microgranules an aqueous suspension of micronized fenofibrate containing ~~the~~surfactant~~,~~ and~~the~~ solubilized binding cellulose derivative~~and the micronized fenofibrate in suspension on neutral microgranules~~.

13. (Cancelled)

14. (Currently Amended) The pharmaceutical composition of claim 3, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 3.6 cP.

15. (Currently Amended) The pharmaceutical composition of claim 1, wherein said fenofibrate is present in an amount greater than or equal to 75% by weight, relative to the weight of ~~the~~said pharmaceutical composition.

16. (Currently Amended) The pharmaceutical composition of claim 1, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of ~~the~~said fenofibrate.

17. (Currently Amended) The pharmaceutical composition of claim 1, wherein said binding cellulose derivative represents between 5 and 12% by weight, relative to the weight of ~~the~~said pharmaceutical composition.

18. (Currently Amended) The pharmaceutical composition of claim 9, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

19. (Currently Amended) The pharmaceutical composition of claim 9, wherein said excipient is selected from the group consisting of lactose, α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)], a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide, and talc.

20. (Currently Amended) The pharmaceutical composition of claim 1, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

21. (Currently Amended) A pharmaceutical composition ~~comprising~~in the form of granules, wherein each granule comprises a neutral microgranule on which is disposed a composition comprising: micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization agent, wherein the mass ratio of said fenofibrate to said binding cellulose derivative is between 5/1 and 15/1.

22. (Currently Amended) The pharmaceutical composition according to claim 21, wherein ~~the~~said binding cellulose derivative is hydroxypropylmethylcellulose.

23. (Currently Amended) The pharmaceutical composition of claim 21, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 18 cP.

24. (Currently Amended) The pharmaceutical composition of claim 21, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 3.6 cP.

25. (Currently Amended) The pharmaceutical composition of claim 21, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

26. (Currently Amended) The pharmaceutical composition of claim 21, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of said fenofibrate.

27. (Currently Amended) The pharmaceutical composition of claim 21, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of said fenofibrate.

28. (Currently Amended) The pharmaceutical composition of claim 21, wherein said pharmaceutical composition further comprises at least one excipient.

29. (Currently Amended) The pharmaceutical composition of claim 28, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

30. (Currently Amended) The pharmaceutical composition of claim 29, wherein said diluent is lactose.

31. (Currently Amended) The pharmaceutical composition of claim 29, wherein said antifoaming agent is α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] or a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide.

32. (Currently Amended) The pharmaceutical composition of claim 29, wherein said lubricant is talc.

33. (Currently Amended) The pharmaceutical composition of claim 21, wherein said micronized fenofibrate has a mean particle size less than 15 μm.

34. (Currently Amended) The pharmaceutical composition of claim 21, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

35. (Currently Amended) The pharmaceutical composition of claim 21, wherein said composition is ~~in the form of granules or powder, optionally~~contained in gelatin capsules.

36– 46. (Cancelled)

47. (Currently Amended) The pharmaceutical composition of claim 2, wherein at least ~~achieving~~95% of said fenofibrate is dissolved~~dissolution in vitro~~ at 30 minutes, as measured using a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N.

EXHIBIT 24

REMARKS

Status of the Claims:

Claims 1-47 were pending in the application. By this amendment, claims 1-7, 9-12, 14-35 and 47 are amended, and claims 13 and 36-46 are cancelled without prejudice or disclaimer.

Claims 1-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,895,726 (Curtet) in view of U.S. Patent No. 6,074,670 (Stamm). The rejection is respectfully traversed.

Substance of the Interview:

Applicants gratefully acknowledge the interview conducted September 20, 2005.

During the interview, the examiner acknowledged that the *in vivo* data presented in the proposed Bobotas Declaration establishes unexpected results in that the claimed pharmaceutical formulations achieve greater bioavailability than those of the prior art, and this is achieved with lower concentration of hydrophilic polymer than that taught by Stamm (the '670 patent).

It was further agreed that patentability would be further supported by amendments reciting that the claimed composition is in granule form and/or by reciting the relative concentrations of the fenofibrate and the binder by reference to their mass ratio (e.g., as in claim 21).

In order to expedite examination, Applicants agreed to withdraw claims 36, 37, and 46, directed to methods of preparing compositions; and claims 38-45 directed to aqueous suspensions, without prejudice or disclaimer.

Supplemental Information Disclosure:

Applicants submit herewith a Supplemental Information Disclosure Statement citing additional art. Applicants do not believe that the newly cited art is more relevant than that relied upon in the outstanding rejection; however, Applicants do not wish to leave any question as to their compliance with 37 CFR § 1.56.

In the interest of expediting examination, Applicants address EP 0 793 958 to Keil et al. Since this application is in German, a full translation of the specification

has been provided herewith. The Keil reference discloses fenofibrate compositions. The compositions are fabricated by a wet granulation method, which produces a composition lacking the granular structure of the instant claims, which require a neutral core coated with fenofibrate, surfactant and binder.

The Keil fenofibrate compositions require cross-linked polyvinylpyrrolidone. See, e.g., page 9, second paragraph ("... in the process of the invention cross-linked polyvinylpyrrolidone must be obligatorily also mixed in."). Cross-linked polyvinylpyrrolidone is not water soluble, which is a requirement of the solubilization adjuvant (binder) of the present invention.

More importantly, the Keil fenofibrate compositions are not granular compositions that comprise a neutral microgranule core. Indeed, Keil expressly distinguishes over a reference describing such a structure. See page 9, second paragraph (distinguishing EP A1 256 933, the European equivalent to U.S. Patent No. 4,800,079, of record).

Keil reports that the resulting formulation "yielded no significant deviation between the present fenofibrate preparation produced in accordance with the invention and the one produced according to example 1 of EP patent 330 532." See page 13, final paragraph. EP '532 corresponds to Curtet (the '726 patent). The present invention, on the other hand, provides for a surprising and unexpected increase in bioavailability as compared to Curtet, as explained to the examiner in the interview, and as further elucidated below.

Thus, Applicants respectfully submit that the newly-cited Keil reference neither anticipates nor renders obvious the present invention.

The Present Rejection:

As noted above, claims 1-13 presently stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Curtet (the '726 patent) in view of Stamm (the '670 patent). As demonstrated to the examiner in the interview, the present invention surprisingly yields greater fenofibrate bioavailability than commercial embodiments of the Curtet and Stamm patents. In the fenofibrate art, increased bioavailability is very important to reduce the dosage of the drug (and thereby reduce

the potential side effects). The following is a short history of fenofibrate dosage forms, which demonstrates this importance.

Fenofibrate is a well-known drug used for the treatment of hyperlipidemia, hypertriglyceridemia and hypercholestemia. Fenofibrate has poor water solubility, and it's absorption in the digestive tract is limited. In the mid-1980's, the daily dose of fenofibrate was as much as 300 mg (3 X 100 mg) (*see* Attachment A, the product insert for LIPIDIL® fenofibrate capsules), which resulted in side effects. Since then, much research has been devoted to decreasing the effective dose of fenofibrate while increasing the bioavailability of the drug. One approach was to decrease the particle size of fenofibrate by micronization, thus permitting faster dissolution and associated absorption in the upper GI tract (fenofibrate is poorly absorbed in the lower GI tract). *See* U.S. Patent No. 4,800,079.

Curtet's '726 patent showed another approach to reduce the daily dose of fenofibrate. The '726 patent describes capsules of a therapeutic composition containing a co-micronized mixture of fenofibrate and a solid surfactant. This technology was employed in TRICOR® fenofibrate capsules, which were available in 67 mg, 134 mg and 200 mg strengths, and were marketed by Abbott Laboratories. (*See* Attachment B, the product insert for TRICOR® fenofibrate capsules; this product has been discontinued.) According to the product insert, one 67 mg capsule containing co-micronized fenofibrate was bioequivalent to one 100 mg capsule containing non-micronized fenofibrate (i.e., a LIPIDIL® capsule). Thus, the effective daily dose of fenofibrate was reduced from 300 mg to 200 mg.

The '726 patent was listed by its manufacturer, Abbott Laboratories, Inc., in the FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the "Orange Book") as covering TRICOR® fenofibrate capsules. (*See* Attachment C, the 2002 Orange Book listing for TRICOR® fenofibrate capsules.) Thus, according to the manufacturer, TRICOR® fenofibrate capsules are a commercial embodiment of the '726 patent.

Stamm's '670 patent reports that, while the '726 patent[1] was an improvement over the 300 mg daily dose of fenofibrate, the '726 patent technology "suffers from

[1] The '670 patent refers to the European equivalent of the '726 patent, namely EP-A-0330532.

several disadvantages." (Column 1, lines 66-67.) The '670 patent deemed itself an improvement over the formulations of the '726 patent.

The '670 patent discloses a fenofibrate composition containing 5-50% fenofibrate, optionally co-micronized with 0-10% of a surfactant, and 20-60% of a hydrophilic polymer. The claims of the '670 patent require 20-45% fenofibrate, optionally co-micronized with 0.1-3% of a surfactant, and 20-45% of a hydrophilic polymer.

The manufacturer introduced a second-generation TRICOR® product, in the form of tablets in 54 mg and 160 mg strengths. (*See* Attachment D, the product insert for TRICOR® fenofibrate tablets, 54 mg and 160 mg; also discontinued.) According to the product insert, the 160 mg TRICOR® fenofibrate tablets are bioequivalent to 200 mg fenofibrate capsules (i.e., a TRICOR® capsule). Thus, the effective daily dose of fenofibrate was reduced from 200 mg to 160 mg.

The '670 patent was listed in the Orange Book by the manufacturer as covering TRICOR® fenofibrate tablets, 54 mg and 160 mg. (*See* Attachment C, the 2002 Orange Book listing for TRICOR® fenofibrate tablets, 54 mg and 160 mg.)[2] Thus, according to the manufacturer, TRICOR® fenofibrate tablets, 54 mg and 160 mg, are a commercial embodiment of the '670 patent.[3]

The LIPIDIL® and TRICOR® family of products described above demonstrate an evolution from higher to lower maximum daily doses of fenofibrate (first 300 mg per day, then 200 mg per day, then 160 mg per day, then 145 mg per day).

The present invention furthers the advances made by the prior fenofibrate formulations covered by the '726 patent and the '670 patent. Unlike the '670 patent formulations, however, the pharmaceutical formulations of the present invention increase the percentage of fenofibrate, and decrease the percentage of binder. The claimed pharmaceutical compositions constitute more fenofibrate relative to binder than the compositions of the '670 patent.

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[2] The '726 patent is also listed; however, the '726 patent claims only cover capsules, not tablets, and therefore the '726 patent is not relevant to this product.

[3] Subsequent to the introduction of 54 mg and 160 mg TRICOR® fenofibrate tablets, the manufacturer introduced a third-generation TRICOR® product in the form of tablets in 48 mg and 145 mg strengths (see Attachment E, the product insert for TRICOR® fenofibrate tablets, 48 mg and 145 mg), thus again reducing the maximum daily dose of fenofibrate, from 160 mg to 145 mg. The '670 patent is not listed in the Orange Book for this third-generation product.

Surprisingly, the combination of a higher percentage of fenofibrate and a lower percentage of binder results in increased bioavailability, and a reduction in the amount of fenofibrate necessary for effective treatment. *See* Bobotas Declaration submitted herewith. Specifically, the claimed formulations provide greater bioavailability on a per-milligram basis than the TRICOR® formulations covered by the '726 patent and the '670 patent.

A commercial embodiment of the present invention is ANTARA® fenofibrate capsules (*See* Attachment F, the product insert for ANTARA® fenofibrate capsules), marketed by Reliant Pharmaceuticals, Inc. According to the product insert, 130 mg ANTARA® fenofibrate capsules are bioequivalent to 200 mg fenofibrate capsules (i.e., a TRICOR® capsule). Thus, with ANTARA®, the maximum daily dose of fenofibrate has been advantageously reduced to 130 mg.

The Bobotas Declaration submitted herewith supports the foregoing. The Bobotas Declaration shows that a commercial embodiment of the claimed invention, 130 mg ANTARA® capsules, has significantly greater bioavailability than a commercially available embodiment of the '726 patent. Specifically, the Bobotas Declaration establishes that, after a single dose, 130 mg ANTARA® capsules have 25.5% greater bioavailability (on a per milligram basis) than 200 mg TRICOR® capsules, which are commercial embodiments of the '726 patent; and at steady state, 130 mg ANTARA® capsules have 37.3% greater bioavailability on a per milligram basis. Bobotas Declaration, ¶¶ 8 and 12.

Likewise, the Bobotas Declaration provides comparative data relative to the '670 patent. Here, Dr. Bobotas compares 120 and 144 mg capsules of the claimed invention to 160 mg TRICOR® tablets, a commercial embodiment of the '670 patent. The Declaration establishes that the embodiments of the claimed invention, i.e., 120 mg and 144 mg capsules, show a 20.0% and 14.7% greater bioavailability, respectively, on a per-milligram basis relative to 160 mg TRICOR® tablets. Bobotas Declaration, ¶ 16.

Applicants respectfully submit that the above remarks and the Bobotas Declaration demonstrate that the present invention achieves surprising and unexpected results. Neither the '670 patent nor the '726 patent teach or suggest that a combination of a higher percentage of fenofibrate and a lower percentage of

polymer would produce an increase in bioavailability, and a decrease in the amount of fenofibrate necessary for effective treatment. This effect is only seen in the claimed invention.

The Examiner has asserted that the '670 patent suggests using hydrophilic polymer in a fenofibrate formulation in the range of 5-40% (citing Col 6, lines 30-40). This is not an accurate reading of the '670 patent. The cited section describes the formulation of a suspension. That suspension is then sprayed onto neutral granules. The composition of the suspension is quite different than the final composition of the pharmaceutical formulation (i.e., the coated granules); and so it cannot be said that this embodiment of the '670 patent teaches or suggests the claimed pharmaceutical formulation, which is in the form of granules.

Indeed, as Applicants have shown, the cited references teach away from the present invention. The '670 patent teaches that to enhance bioavailability and thereby produce an effective formulation of reduced dosage, one must use at least 20% by weight hydrophilic polymer by weight of the composition ('670, col. 3, lines 11-23); and fenofibrate up to 50% by weight of the composition ('670, col. 5, lines 3-4). In contrast, Applicants' claimed granules contain 2-15% by weight of binder, and at least about 60% by weight fenofibrate; and, most surprisingly, in doing so the invention achieves substantially greater bioavailability and more rapid dissolution. This is the hallmark of non-obviousness and thus, patentability.

CONCLUSION

The Bobotas Declaration and the above remarks establish patentability for at least two reasons. First, the claimed compositions are contrary to conventional wisdom, which held that enhanced bioavailability, and reduced dosages, could be achieved only by diluting fenofibrate in binder. Instead, the claimed compositions achieve greater bioavailability by increasing the mass ratio of fenofibrate relative to binder. This results in lower effective doses, which reduces potential side effects and promotes patient compliance.

Second, the claimed compositions have surprisingly greater bioavailability compared to commercial fenofibrate formulations. In both single dose studies and at steady state, the claimed fenofibrate formulations showed greater bioavailability on a

per-milligram basis as compared to commercial formulations covered by the '726 patent and the '670 patent.

In view of the foregoing amendments and remarks, applicants request reconsideration and withdrawal of all outstanding rejections in favor of a formal notification of allowance. If, however, the Examiner perceives any impediments to such notification of allowance, whether formal or substantive, Applicants encourage the Examiner to call their attorney at the number provided below. Such informal communication will expedite examination and disposal of the application.

Respectfully submitted,

BUCHANAN INGERSOLL PC (INCLUDING ATTORNEYS FROM BURNS DOANE SWECKER & MATHIS)

Date: October 21, 2005

By: _____
Brian P. O'Shaughnessy
Registration No. 32,747

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

EXHIBIT 25

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Bruno CRIERE et al.

Serial No.: 10/030,262 Group Art Unit: 1615

Filed: April 17, 2002 Examiner: Channavajjala, L. S.

For: PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND THE PREPARATION METHOD

SECOND DECLARATION OF GEORGE BOBOTAS, Ph.D., UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, George Bobotas, Ph.D., hereby declare and affirm that:

1. I am the same person that submitted a Declaration dated October 21, 2005 (October 21st Declaration or "Bobotas I") in support of the referenced patent application.
2. It is my understanding that the Examiner has requested clarification with respect to the composition of the test formulations described in the October 21st Declaration.
3. In my October 21st Declaration, I presented the results of three studies: A, B and C. Studies A and B assessed the relative bioavailability of 130 mg ANTARA® fenofibrate capsules of the invention versus 200 mg TRICOR® fenofibrate capsules. Study C assessed the relative bioavailability of 120 mg and 144 mg fenofibrate capsules of the invention versus 160 mg TRICOR® fenofibrate tablets.

Fenofibrate Capsules of the Invention

4. The 120 mg, 130 mg and 144 mg fenofibrate capsules of the invention utilized in Studies A, B, and C, each contained granules of the same composition. The granules are 64% by weight fenofibrate, relative to the weight of the granules; and 12% by weight binding cellulose derivative, relative to the weight of the granules.

200 mg TRICOR® Fenofibrate Capsules

5. The composition of the 200 mg TRICOR® fenofibrate capsules is described in the product insert (Attachment A, the first page of the product insert for 200 mg TRICOR® fenofibrate capsules), and in U.S. Patent No. 4,895,726 (Attachment B).[1] According to the product insert, 200 mg TRICOR® fenofibrate capsules contain the following inactive ingredients: crospovidone (i.e., crosslinked polyvinyl pyrrolidone), iron oxide, lactose, magnesium stearate, pregelatinized starch, sodium lauryl sulfate and titanium dioxide.
6. None of the ingredients utilized in the 200 mg TRICOR® fenofibrate capsules are described as binders in the Curtet ('726) patent.
7. I supervised an analysis of the 200 mg TRICOR® fenofibrate capsules to ascertain the weight percentage of fenofibrate in the formulation. 10 capsules (Lot # 727552E21) were opened and the contents were weighed. Dividing this amount by the number of capsules gave the average weight of the formulation in each capsule. The average weight of the formulation in each capsule was 343 mg. Thus, assuming that each capsule contained 200 mg fenofibrate, the formulation of the 200 mg TRICOR® fenofibrate capsules is about 58% fenofibrate by weight, relative to the weight of the formulation.

[1] *See, Bobotas I*, fn. 2 (the Curtet ('726) patent is listed by the distributor of TRICOR® in FDA's Orange Book as covering the product).

160 mg TRICOR® Fenofibrate Tablets

8. The composition of the 160 mg TRICOR® fenofibrate tablets is described in the product insert (Attachment C, the first page of the product insert for 160 mg TRICOR® fenofibrate tablets), and in U.S. Patent No. 6,074,670 (Attachment D).[2] According to the product insert, 160 mg TRICOR® fenofibrate tablets contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone (i.e., polyvinyl pyrrolidone), sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide and xanthan gum.
9. I supervised an analysis of the 160 mg TRICOR® fenofibrate tablets to ascertain the weight percentage of fenofibrate in the formulation. 90 tablets (Lot # 02-8333R1) were weighed. Dividing this amount by the number of tablets gave the average weight of each tablet. The average weight of each tablet was 712 mg. Thus, assuming that each tablet contained 160 mg fenofibrate, each 160 mg TRICOR® fenofibrate tablet contains 23% fenofibrate by weight, relative to the weight of the tablet.

[2] *See, Bobotas I*, fn. 3 (the Stamm ('670) patent is listed by the distributor of TRICOR® in FDA's Orange Book as covering the product).

I, George Bobotas, Ph.D., hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent(s) issuing therefrom.

Date: 2/14/06

George Bobotas, Ph.D.

George Bobotas, Ph.D.

EXHIBIT 26

REMARKS

Claims 1-7, 9-12, 14-35 and 47 are pending, and are presented for reconsideration. No amendments have been made to the claims.

The pending claims stand rejected over the Curtet ('726) patent and the Stamm ('670) patent. In the Office Action (page 3), the Examiner acknowledged that the *in vivo* bioavailability data for the claimed fenofibrate formulations was superior to the commercial formulations of Curtet and Stamm. To complete the record, however, the Examiner requested that applicants set forth the actual percentages of fenofibrate and binding cellulose derivative in the test formulations of the invention. Such data is supplied herewith, and described below.

Applicants submit herewith the Second Declaration of George Bobotas, Ph.D., Under 37 CFR § 1.132 ("*Bobotas II*"). That Declaration is supplemental to the first declaration of Dr. Bobotas, dated October 21, 2005 ("*Bobotas I*"). *Bobotas II* shows that the 120 mg, 130 mg and 144 mg formulations described in *Bobotas I* are within the instant claims; and those of the 200 mg and 160 mg TRICOR® formulations are outside the instant claims.

Instant claim 1 requires, among other things, a pharmaceutical composition wherein fenofibrate is present in an amount greater than or equal to 60% by weight, relative to the weight of said pharmaceutical composition, and further wherein a binding cellulose derivative represents between 2 to 15% by weight, relative to the weight of said pharmaceutical composition. Instant claim 21 requires, among other things, a pharmaceutical composition wherein the fenofibrate and the binding cellulose derivative are present in a mass ratio of between 5/1 and 15/1.

130 mg ANTARA® capsules v. 200 mg TRICOR® capsules (Curtet ('726) patent):

Bobotas II shows that the formulation of the 200 mg TRICOR® capsules of the Curtet ('726) patent is 58% fenofibrate by weight, relative to the weight of the formulation. *Bobotas II*, ¶ 7. Thus, the formulation of the 200 mg TRICOR® fenofibrate capsules of the Curtet ('726) patent are outside the instant claims.[1]

The 130 mg ANTARA® formulation of the invention is 64% fenofibrate by weight relative to the weight of the granules, and 12% by weight binding cellulose derivative, relative to the weight of the granules. *Bobotas II*, ¶ 4. Thus, the 130 mg ANTARA® formulation is within the instant claims.

As was shown in *Bobotas I*, the 130 mg ANTARA® formulation of the instant claims yields surprising and unexpected results as compared to the 200 mg TRICOR® formulation of the Curtet ('726) patent. The 130 mg ANTARA® capsules produced 25.5% greater bioavailability per mg fenofibrate than that of the 200 mg TRICOR® fenofibrate capsules following consumption of a therapeutic lifestyle change (TLC) meal (*Bobotas I,* ¶ 8 and Table 2); and it produced 37.3% greater bioavailability per mg fenofibrate at steady state (*Bobotas I*, ¶ 12 and Table 4).

[1] Applicants are unable to determine the weight percent, if any, of binder in the 200 mg TRICOR® formulation. The Curtet ('726) patent does not describe any of the ingredients used in that formulation as "binders." *Bobotas II*, ¶ 6. Nonetheless, the 200 mg TRICOR® capsule formulation is outside the scope of instant claim 1 for at least the following reasons: 1) it has less than 60% by weight fenofibrate relative to the weight of formulation; and 2) it does not use a neutral microgranule.

120 mg and 144 mg capsules v. 160 mg TRICOR® tablets (Stamm ('670) patent):

Bobotas II shows that the 160 mg TRICOR® fenofibrate tablets of the Stamm ('670) patent are 23% fenofibrate by weight, relative to the weight of the tablet. *Bobotas II*, ¶ 9. Thus, the 160 mg TRICOR® fenofibrate tablets of the Stamm ('670) patent are outside the instant claims.[2]

The 120 mg and the 144 mg formulations of the instant claims are 64% by weight fenofibrate relative to the weight of the granules, and 12% by weight binding cellulose derivative, relative to the weight of the granules. *Bobotas II,* ¶ 4. Thus, as with the 130 mg ANTARA® formulation, the 120 mg and the 144 mg formulations are within the instant claims.

Applicants have previously shown that in comparison to the 160 mg TRICOR® tablets of the Stamm ('670) patent, the 120 mg and 144 mg formulations of the instant claims have 20% and 14.7% greater bioavailability per mg fenofibrate, respectively. *Bobotas I,* ¶ 16 and Table 6. Accordingly, the formulations of the instant claims produce surprising and unexpected results in enhanced bioavailability per mg fenofibrate.

Applicants respectfully submit that the record is now complete and that the Examiner should give full weight to the comparative evidence provided in *Bobotas I*.

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants

[2] Again, Applicants are unable to determine the weight ratio of any binder in the 160 mg TRICOR® tablet. Nonetheless, the 160 mg TRICOR® formulation is outside the scope of instant claim 1 if only because it has less than 60% by weight fenofibrate relative to the weight of the pharmaceutical composition. In addition, the Stamm ('670) patent requires formulations having at least 20% hydrophilic polymer (Stamm at col. 3, lines 13-23, and claim 1). Thus, it would appear that the 160 mg TRICOR® formulation is outside the scope of instant claim 1 because it does not have between 2 to 15% by weight binding cellulose derivative relative to the weight of the pharmaceutical composition.

submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

BUCHANAN INGERSOLL PC

Date: Feb. 21, 2006

By: _____
Brian P. O'Shaughnessy
Registration No. 32,747

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EXHIBIT 27

Office Action Summary	Application No.	Applicant(s)	
	10/030,262	CRIERE ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-12,14-35 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-12,14-35 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of response and declaration dated 2-21-06 is acknowledged.

Claims 1-7, 9-12, 14-35 and 47 are pending. Claims 8, 13 and 36-46 have been canceled.

Response to Amendment

Upon careful consideration, the finality of the rejection of the last Office action is withdrawn. However, the following new rejection is applied.

Claim Rejections - 35 USC § 103

Claims 1, 4-6, 9-12, 15-21, 23-35 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,800,079 to Boyer in view of EP 793958 (hereafter EP, submitted on PTO-1449) OR EP in view of Boyer.

Boyer teaches granular fenofibrate compositions comprising fenofibrate wherein each granule comprising an inert core, coated with fenofibrate, and a protective layer. Boyer teaches that the fenofibrate is present in the form of crystalline microparticles of dimensions not greater than 30 microns, and preferably less than 10 microns (abstract). Boyer teaches that the outer protective layer is formed of a substance selected from the group consisting of cellulose polymers, methacrylic polymers, polyvinylpyrrolidone etc., which forms a matrix and the fenofibrate sprayed as a powder is deposited into the polymer matrix (claims). While, Boyer does not specify the percentage of fenofibrate, the example formulation in col. 3 of Boyer shows a high amount of fenofibrate (upto 80% of the formulation). Boyer further teaches incorporation of excipients such as lactose, starch, glucose etc in the composition (claims). Thus, Boyer teaches the

claimed cellulose polymers and excipients and high amounts of fenofibrate, as in claim 1, 4, 9, 10, 15, 18-20 and 28-34. Boyer fails to teach a surfactant in the composition.

EP teaches a fenofibrate composition comprising fenofibrate, surfactant and polyvinylpyrrolidone and other adjuvants, prepared by mixing, granulating and subsequent drying (abstract). EP teaches that the composition does not require a co-micronization of fenofibrate and surfactant and instead can be prepared by mixing fenofibrate particles with PVP and then with surfactants as well as other adjuvants (page 6). With respect to the claimed amount of surfactant, EP teaches a minimum amount of 1.5% of surfactant (page 7), which is within the range of claims 6 and 26. EP also teaches the claimed (claims 5, 25) surfactants such as sodium lauryl sulfate (page 10, 11). EP also teaches fenofibrate as high as 70% to 80% and 10-30% polyvinylpyrrolidone. Further, EP teaches preparing fenofibrate in the form of capsules and hence meets the claimed capsules.

Accordingly, it would have been obvious for one of an ordinary skill in the art at the instant invention to use a surfactant (of EP) in preparing fenofibrate composition of Boyer by mixing the surfactant (without co-micronization with the drug) with micronized fenofibrate because EP suggests such mixing of surfactant reduces the micronization volume of surfactant (as opposed to co-micronizing the drug and surfactant) and results in good bioavailability. Boyer fails to teach the claimed percentage of cellulose polymer, specific viscosity of the cellulosic polymer and the ratios of fenofibrate to polymer. However, Boyer teaches cellulose polymers and PVP as equivalent in forming inert matrix and EP teaches the percentages of PVP in the same range as claimed.

Accordingly, in the absence of any unexpected results, with respect to claimed percentage of cellulose polymer it would have been within the scope of a skilled artisan to employ cellulose (or PVP) as a binding polymer, in compositions comprising high amounts of fenofibrate, surfactants and other adjuvants, at a concentration suggested by EP with an expectation to provide a supporting and binding matrix for fenofibrate. Alternatively, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use cellulose polymer of Boyer in the composition containing high amounts of fenofibrate, adjuvants and surfactant of EP, because Boyer suggests cellulose polymers as equivalent with PVP in providing matrix support and as binders. With respect to the claimed release rate, the burden is shifted to applicants show that the prior art teachings do not provide the claimed release rate.

Claims 2, 3, 7, 14 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyer in view of EP 793958 as applied to claims 1, 4-6, 9-12, 15-21 and 23-35 above, and further in view of WO 96/01621 (hereafter WO, submitted on PTO-1449).

The teachings of Boyer and EP have been discussed above. Boyer teaches cellulose polymers in the fenofibrate composition but neither reference teach the specific cellulose polymer of the instant claims.

WO teaches a controlled release composition for insoluble drugs, containing a core around which is coated a drug-containing layer. WO teaches that addition of a hydrophilic polymer in the drug-containing layer, gives favorable mechanical properties

and also a control in the release of the drug upon filling into capsules or sachets (page 4). The process of applying the drug and polymer on the core is described on page 4, lines 20-29. Among the hydrophilic polymers suitable for layering, WO teaches PVP, cellulose derivatives such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, carboxymethylcellulose, methylcellulose etc (page 5, lines 6-12). WO suggests a ratio of active substance to polymer in the range of 10:1 to 1:2 or 5:1 to 1:1, which includes the ratios of instant claims.

While WO does not teach fenofibrate of the instant claims, WO teaches compositions suitable for water insoluble drugs, which includes fenofibrate of Boyer and EP. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use cellulose polymers such as HPMC of WO in the fenofibrate composition of Boyer and EP because WO suggests cellulose polymers such as ethylcellulose and HPMC impart permeability to the coating layer (page 7, lines 18-21). WO further suggests that hydrophilic polymers act as binders and give the composition plastic properties, yield a controlled release that independent of pH. Accordingly, one of an ordinary skill in the art at the time of the instant invention would have expected to increase the plasticity of the fenofibrate composition of Boyer and EP and achieve a pH independent controlled release of fenofibrate with the cellulose polymers in the composition.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 9-12, 14-35 and 47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-45 of copending Application No. 10/677,861 (PGPUB 2004/0137055). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims as well as the patented claims are directed to compositions comprising 60% or greater than 60% micronized fenofibrate, surfactant and a binding cellulose derivative. While instant claims recite the composition as containing a neutral granule in which a core is coated with fenofibrate, surfactant and binding cellulose, copending application claim the composition and also claim the instant method of preparing the same. Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare the instant composition by the method of the copending claims because the copending composition also claims a composition with the same components and accordingly, one of an ordinary skill in the art would have expected the same therapeutic efficacy.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-7, 9-12, 14-35 and 47 are directed to an invention not patentably distinct from claims 1-45 of commonly assigned 10/677,861. Specifically, as explained above, the copending application also describes a micronized fenofibrate composition employing cellulose binding polymer and a surfactant, wherein the ratios and the percentages of the components are the same. Further, the copending application also teaches the method of preparing the instant composition.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/677,861, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon

the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments

Applicant's arguments filed 2-21-06 have been fully considered but they are not persuasive.

The previous rejection of instant claims over Stamm and Curtet references has been withdrawn. Applicants filed a second declaration of George Bobotas, to support the unexpected results provided in the first declaration (dated 10-21-05). With respect to the first declaration, examiner stated that the results were not commensurate with the scope of the claims because the commercial formulations used for comparison does not describe the percentages of fenofibrate and cellulose polymers, and that instant claims differ from the prior art teachings in the percentages of fenofibrate and cellulose polymers. In response, applicants (in the second declaration) now calculated the percentages of fenofibrate of commercial formulations of the instant invention and prior art teachings. It is submitted that in all the examples the fenofibrate percentage was lower than the claimed range, whereas the inventive commercial formulation (ANTARA) comprises 64% fenofibrate and 12% binding cellulose derivative. It is argued that the 130 mg ANTARA capsule formulation results in surprising and unexpected 25.5% increase in bioavailability compared to 200 mg TRICOR capsules, on a per mg

fenofibrate basis. Similarly, applicants argued that the 120 and 144mg ANTARA capsules showed an 20% and 14.7% increased bioavailability respectively, when compared to 160 mg TRICOR tablets of Stamm et al that contained 23% fenofibrate.

The unexpected results presented are not commensurate with the scope of the instant claims for the following reasons:

Instant claim 21 is an interdependent claim, which only recites the ratios of fenofibrate and the cellulose polymer and not the percentages as used in comparative data. Further, applicants provided no information of what are the ratios in the commercial ANTARA formulation and if they are commensurate with those claimed. With respect to the percentages of fenofibrate and cellulose polymers in claim 1, the comparative formulation employs polyvinylpyrrolidone and not cellulose polymers. Thus, the comparative results have two variables – percentages of fenofibrate and two different polymers. Accordingly, the observed increase in bioavailability could be attributed to a difference in the percentages of fenofibrate or dependent on the type of polymer (cellulose versus PVP) used or both, and not solely to the percentage of fenofibrate. However, instant claims are limited to only cellulose polymers and accordingly, the comparative evidence is outside the scope of the instant invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lakshmi S Channavajjala
Examiner
Art Unit 1615

March 8, 2006